Author’s response to reviews

Title: Reduced level of arousal and increased mortality in adult acute medical admissions: A systematic review and meta-analysis

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Response Letter

Dear Leon Flicker,

We would like to thank the reviewers for their comments on the manuscript which we address in turn below. We believe that by addressing them the manuscript is improved, and hope it is now suitable for publication in BMC Geriatrics. We are happy to answer any further queries you or the reviewers have.

Yours sincerely,

Samantha Blackley on behalf of all authors.
Reviewer 1: Gideon Caplan

Major issues.

1. “The idea behind meta-analysis is that individual studies may show conflicting results or not have the statistical power to uncover some "hidden" truth that only meta-analysis can elucidate. I cannot recall ever seeing a meta-analysis where every single study included in the analysis has already found the phenomenon being studied significantly changed and all in the same direction, as can be seen in the Forest plot in figure 2. To me, this means that leaving the results at that is to waste the readers time. Not to mention reviewers. The authors should feel morally compelled to add value to the existing data. Whether that be by some sort of meta-regression analysis or putting more thought into the whole exercise and coming up with other clever ideas, I don't mind.”

Response: We agree that meta-analysis often looks to identify conflicting results, or summing up multiple small, statistically insignificant, studies, but it is also well recognised that meta-analysis can confirm the robustness of an effect size across multiple studies. “If a treatment effect (or effect size) is consistent across the series of studies, these procedures [meta-analysis] enable us to report that the effect is robust across the kinds of populations sampled, and also to estimate the magnitude of the effect more precisely than we could with any of the studies alone. If the treatment effect varies across the series of studies, these procedures enable us to report on the range of effects, and may enable us to identify factors associated with the magnitude of the effect size.” (Introduction to Meta-analysis, M Borenstein, LV Hedges, JPT Higgins, HR Rothstein 2011, Wiley Publishers. P1)

The reason for presenting the forest plot as we did was to show that the effect size did not vary significantly by admission type, by study size or risk of bias, i.e. to illustrate the remarkable consistency despite the range of study designs, populations and settings etc.

Our view is that a meta-regression would not help here. There are limited data available on potential confounders, these are provided in different ways in different studies, and only in aggregated summary statistics. Therefore we believe performing meta-regression in an internally consistent manner is not possible, and there is a serious risk that trying to do such an analysis would give spurious results Overall, this unfortunately means that meta-regression would not strengthen the paper. Note that we did contact authors for additional information, but neither data on these potential confounders was not collected or not available.
Our main message is that drowsiness is a poor prognostic sign and linked to delirium. The magnitude of this effect, and its consistency across studies, is remarkable. This point may be self-evident to experienced clinicians, but the delirium literature lacks studies including people with reduced level of arousal (hypoactive delirium), and the emergency medicine literature lacks studies which consider delirium in people with reduced level of arousal. We suggest that medical staff should assess patients with reduced level of arousal explicitly for delirium and inform patients/families and treat accordingly. It is essential that future studies include level of arousal, along with detailed delirium assessments and collection of data on confounders, to add value to these analyses.

We also performed a sensitivity analysis of studies which used GCS vs those that used other scales, see comment to reviewer 2 below.

To address these comments, we have added these points to the discussion: “We felt it was important to perform a meta-analysis on these studies to confirm the underlying effect size” page 10 line 203 and “Meta-regression was not performed due to heterogeneity of studies” page 10 line 212.

2. “Despite point 1 the analysis, as shown in figure 2, was associated with significant heterogeneity. The authors should mention that in the results, and state which analysis was used, fixed or random effects, and also discuss why there was heterogeneity.”

Response: We state in Methods: Synthesis of results page 6 line 121 that we used a random effects model. We have added the sentence “In light of predicted significant heterogeneity, a random effects model was used in the meta-analysis.” page 11 line 232. We state in Discussion: Summary of findings page 9 line 213 “These findings have important caveats in that the included studies were heterogeneous in the populations studied and methods used to measure level of arousal” and again mention clinical heterogeneity in limitation of the review page 11 line 243.

We have added to results: Quantitative result “There is significant heterogeneity with an I^2 of 64%. This is most likely due to the variation in medical conditions studied and range of scales used.” Page 8 line 167.
Minor issues

1. “P.3 The introduction demurely says that "Some studies report that reduced level of arousal is associated with mortality." This suggests to me that some do not. Were there actually any studies that that showed reduced arousal was associated with reduced mortality?”

Response: We thank the reviewer for noting this. It is correct that we did not identify any studies that showed reduced arousal association with reduced mortality. We have removed ‘Some studies have reported that’ and the sentence now reads “Reduced level of arousal is associated with mortality” Page 3 line 52.

2. “P.9 Astonishingly, given point 1 above in the Major issues, the authors summarised the findings as only suggesting that patients with reduced arousal have a higher level of mortality. I think the evidence supports a stronger conclusion.”

Response: Thank you. We have substituted the word ‘suggests’ with ‘demonstrates’. Page 9 line 199.

Reviewer 2: Mark William Yates

1. “The method is well described and appropriate for this systemic review. The authors rightly comment on the heterogeneity of the reporting of arousal, low quality of evidence and the potential for significant bias. I wonder if this could be mitigated by restriction of years in the inclusion criteria - assuming awareness and use of scales for arousal have improved over time.”

Response: We thank the reviewer for these positive comments. We were interested in the suggestion that the scale used may have influenced the results, and have performed a sensitivity analysis of GCS v non-GCS. 11 studies use GCS (6 which could be included in meta-analysis) and GCS is probably the most widely used scale of arousal in clinical practice, and has not changed over the years. We feel that using an arbitrary year restriction would not be useful as there is no evidence of a change of practice around any particular year. This information has been included in the methods: synthesis of results page 6 line 123: “A sensitivity analysis was
performed including only those studies which used the Glasgow Coma Scale to evaluate level of arousal” and results page 8 line 172: “Sensitivity analysis including only those studies using GCS confirmed the direction of the observed effect with a pooled OR of 9.16 (95%CI 6.37-13.18; 7,381 patients, low quality evidence due to risk of bias and clinical heterogeneity).” and discussion page 10 line 204: “Sensitivity analysis including only those studies using GCS- the most widely used clinical arousal test, which has been in use without change for several decades- confirmed the direction of the observed effect with a pooled OR of 9.16. This was performed to reduce the degree of heterogeneity but note significant clinical heterogeneity remains. The studies not included in the meta-analysis showed similar results.”

2. “While I accept the statistical outcome of association, which confirms existing clinical knowledge, I think the clinical relevance of the statistical outcome should be explored in the discussion.”

Response: Thank you. We have expanded this sentence in discussion, interpretation and implications for clinical practice and further research page 12 line 261: “Given the 5.7-fold increased risk of in-hospital mortality in this group clinicians need to be vigilant regarding these patients, consider discussion around prognosis with patients and families, and actively seek evidence to diagnose delirium and manage it appropriately.” We have also discussed comparison to high lactate page 11 line 223.

3. “It would seem that the means of the GCS in the died versus survived are close and the CI approached 1 at the upper end suggesting there would be considerable overlap.”

Response: In the studies which could not be included in the meta-analysis, GCS was classified in different ways (eg low v high, with different cut offs, or continuous scale), and outcomes presented in different ways. We provided these data to show that even for studies not in the meta-analysis, the results were in the same direction. We agree that they should be interpreted with caution and have added to the discussion “Studies not included in the meta-analysis showed results in the same direction, but some upper confidence intervals were close to one, suggesting some overlap between the group. This occurred in three studies. These studies were generally small and used different cut-offs to determine low and high GCS.” Page 10 line 208.
4. “It would, if comparing arousal to lactate and hypotension be helpful to comment not just on mortality OR but the CI of these comparison clinical markers of mortality. Over all I think the conclusion are reasonable.”

Response: Thank you, we have added the CI OR 4 (95% CI 1.7 to 14.1) and hypotension OR 2.0 (CI 1.3 to 2.8) page 10 line 225.